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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/738,049	12/15/2000	David R. Kaplan	071957-0903	2323

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 12/30/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/738,049	KAPLAN, DAVID R.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed on 10/16/2003 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claims 34-61 are cancelled.

2. Claims 1-33 are currently under examination.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-5, 10, 14-18, 25-26, 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karkmann et al. (J. Immu. Methods. 1999) in view of Koester et al. (J. Immunol. Methods 2000 243: 99-106)

Karkmann et al. teach a method of detecting intracellular analyte by applying tyramine-based amplification signal in flow cytometry. Karkmann et al teach fixing and pemeabilizing blood cells with 0.5 saponin, and resuspend the cells in a buffer containing bovine serum albumin. (page 114, Right column to page 115, Left column) Karkmann et al teach staining the cells with fluorescein-labeled antibodies against the analyte which is linked to horseradish-peroxidase directly or indirectly by biotinylation, i.e. avidin-biotin, and thereafter adding tyramine substrate. (page 115, Right column) However, Karkmann et al. do not specifically disclose using an immunoglobulin (isotype or subtype matched antibody) that does not specifically bind to the intracellular analyte as a standard negative control and have at least 10-fold greater signal than the standard negative control.

Koester et al. teach various protocols in measuring intracellular analytes encountered by conventional flow cytometry. (page 99, left column, fist paragraph; See abstract) Koester

et al. teach using an isotype-matched negative control antibody, i.e. closely matched in all properties to the specific antibody, to determine the nonspecific background staining. (page 102, see section 4.2) Koester et al. also urges that "always use negative isotype-matched controls" to insure staining specificity. (page 104, left column, first paragraph) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided Karman et al. with the negative control isotype-matched antibody as taught by Koester et al. to insure the staining specificity since it is well-known in the art.

With respect to claims 1-4, the 10, 20, or 50-fold greater signal compared to that of the standard flow cytometry, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have a reasonable expectation of success because the prior art teaches that tyramide amplification methods often vary according to the type of the cell sample being analyzed and various matrices and parameters appear to work equally well.

4. Claims 1-5, 11-19, and 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lollini et al. (Immunological Blackboard, 1998) in view of Koester et al..

Lollini et al. teach a method and kit for detecting intracellular analyte, i.e. p53, in osteosarcoma cells wherein flow cytometric detection is performed after tyramide signal

amplification (Abstract). Lollini et al. also teach culturing cells in fetal bovine albumin, fixing cells with methanol, and permeabilizing cells with methanol or acetone. Lollini et al. also teach similar tyramide amplification by using an antibody against the analyte, then adding peroxidase-conjugated F(ab')2 anti-mouse IgG, and subsequently placing fuorescein tyramide sustrate to catalyze the deposition of tyramide on cells for detection. Lollini et al. do not specifically teach using isotype/subtype immuglobulin as a standard negative control in the assay. Nonetheless, Lollini et al. recognize a potential problem for this report: "[t]he main problem appeared to be a high level of spontaneous activation and *non-specific binding* of the fluorescent substrate to live cell membranes." (See Conclusion)

Koester et al. teach various protocols in measuring intracellular analytes encountered by conventional flow cytometry. Supra. Koester et al. teach using an isotype-matched negative control antibody, i.e. closely matched in all properties to the specific antibody, to determine the nonspecific background staining. Supra. Koester et al. also urges that "always use negative isotype-matched controls" to insure staining specificity. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided Lollini et al. with the negative control isotype-matched antibody as taught by Koester et al. to insure the staining specificity since it is well-known in the art.

Similarly, with respect to the 10, 20 and 50 fold greater signal as recited in claims 1-4, it has been discussed before in this Office Action, and it would be a reasonable expectation to one skill in the art to incorporate the "isotype-matched" antibody to increase the detection specificity in the flow cytometry assay.

Response to Applicant's Arguments

5. Applicant's arguments with respect to claims 1-33 have been considered but are moot in view of the new ground(s) of rejection.

Enhancement of signal by isotype-matched antibody

Examiner indicates that both Karman and Lollini et al. references do not explicitly teach using isotype-matched antibody for negative control. Examiner cites a secondary Koester et al. reference providing the isotype-matched antibody negative control commonly used in the art of flow cytometry in detecting intracellular analyte. With respect to the enhancement of the signal, the instant claims 1-4 recite an overall greater magnitude, e.g. 10, 20, or 50 fold, of detection in the sample. Both Karman and Lollini et al. references have results of 10-15 fold increase of signal by use of tyramide-based amplification, albeit without the aid of isotype-matched antibody negative control. It would have been obvious to one having ordinary skill in the art to have a reasonable expectation of success in achieving the greater signal as recited in the

instant applications, i.e. 20-50 fold, when incorporating with a more specific and accurate "isotype-matched antibody negative control" as taught by the reference of Koester et al.

Allowable Subject Matter

6. Claims 6-9, 20-22 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

7. The following is a statement of reasons for the indication of allowable subject matter: no prior art teaches or suggests that incubating cells with analyte specific antibodies for flow cytometry assay using 50% or 95% fetal calf serum. The closest prior art is the Ross reference (US 5674694), but the reference teaches a cryopreservation (cold treatment) of cells by using 50% fetal calf serum.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 703-306-4086. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 703-305-3399. The fax phone number for the organization where this application or proceeding is assigned is 703-746-9434.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-305-3399.

Jacob Cheu

Examiner

Art Unit 1641

December 22, 2003

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

12/24/03